ORIGINAL RESEARCH

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Atrial Electromechanical Delay and Diastolic Dysfunction in Primary Sjögren Syndrome

Abstract

Purpose: In this study we aimed to investigate myocardial function and atrial electromechanical properties by conventional and tissue doppler echocardiography in patients with primary Sjögren syndrome.

Methods: Forty patients with Sjögren syndrome (SS) and 25 age- and sex-matched healthy volunteers were enrolled in the study. Using transthoracic echocardiography, myocardial performance index and atrial electromechanical properties were measured.

Results: Basal characteristics were similar between two groups. Myocardial performance index values were disturbed in patients with Sjögren syndrome (0.41 vs. 0.32, $p<0.01$). There was significant intraatrial (16.4 ± 6.4 , 5.0 ± 4.5 , $p<0.01$) and interatrial (30.6 ± 10.1 , 15.4 ± 5.9 , $p<0.01$) electromechanical delay in this patient group.

Conclusion: Myocardial function is disturbed and there is significant atrial electromechanical delay in patients with primary SS. This study is the first to show altered myocardial function and atrial electromechanical properties in primary SS.

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Sjögren syndrome (SS) is a systemic autoimmune disease that primarily affects lacrimal and salivary glands. [1] Because it is a systemic disease, SS may cause different organ involvement and different clinical manifestations. [1-5] SS is relatively frequent, with a prevalence of 0.05-4.8% and is primarily seen in middle aged women. [2,6,7] It can be primary or secondary to another connective tissue disease such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE). [8]

There are substantial data in the literature about the untoward effects of connective tissue diseases on the cardiovascular system: Levendoglu et al. showed ventricular dysfunction in RA patients [9], Rexhepaj et al. showed that left ventricular diastolic dysfunction in RA patients can present even in the absence of clinically evident cardiovascular disease [10], and Cacciappuoti et al. showed disturbed myocardial performance index in SLE patients. [11]

There is some evidence concerning the role of inflammatory status on cardiac dysfunction in the literature. Different diseases may act on the cardiovascular system through the activity of mediators of inflammation. [12-14] A similar association is also found between inflammation and supraventricular arrhythmias. [15]

Although data about how cardiovascular system is affected in SS is limited, left ventricular systolic and diastolic dysfunction, pericardial effusion, pulmonary hypertension and valvular dysfunction have all been reported in patients with SS. [8,16] Abnormalities in the conduction system and also in cardiomyocytes was shown by Inoue et al. and this may indicate that SS patients may be more prone to arrhythmias. [17]

The purpose of this study is to further characterize the changes in the cardiovascular systems of SS patients by measuring both ventricular function and atrial electromechanical properties using conventional and tissue doppler echocardiography.

Materials and Methods

Forty patients with primary SS and 25 age- and sex-matched healthy volunteers were enrolled in the study. American-European consensus criteria for primary SS [18] were accepted as diagnostic criteria. Any disease other than primary SS was accepted as an exclusion criterion (including hypertension and diabetes mellitus). Basal characteristics of all patients were recorded. Laboratory investigations (including hemogram, creatinine, lipid panel, hsCRP, anti SS-A/Ro and anti SS-B/La autoantibodies) were also performed.

Our study was approved by the local ethics committee and informed consent was obtained from all patients and healthy volunteers before enrollment in the study.

Echocardiography

Echocardiographic evaluation of patients was performed using a Vivid 7 echocardiography system (General Electric, Horten, Norway) with a 2.5-5 MHz transducer. Echocardiographic examinations were performed by an experienced cardiologist who was blind to the patients and their characteristics. Patients were evaluated in the left lateral decubitus position. Through all examinations a continuous one lead ECG was recorded. All parameters were calculated as the average of three consecutive beats. Dimensions of left ventricle (LV), septal wall (SW) and posterior wall (PW) thicknesses were measured by M-mode echocardiography in parasternal long axis view and LV ejection fraction (EF) was measured by modified Simpson's method.

For calculation of myocardial performance index (MPI) or Tei index [19], both conventional method (cMPI) and tissue doppler method (tdMPI) were used. MPI was calculated according to following formula: [Isovolumic relaxation time (IVRT) + isovolumic contraction time (ICT)]/ejection time (ET).

To determine the electromechanic characteristics of the atria, tissue doppler was used. For all measurements, the apical four-chamber view was used. Myocardial systolic (S), early diastolic (E) and atrial systolic (A) waves were measured by pulsed wave (PW) doppler and E/A ratio was calculated. PW doppler measurements were then made at the lateral mitral annulus, septal mitral annulus and right ventricular (RV) tricuspid annulus. Time from the beginning of the P wave on the surface ECG to the beginning of the A wave was used as the PA interval and represented the atrial electromechanical delay. This time interval was calculated for lateral mitral annulus (lateral PA), septal mitral annulus (septal PA) and RV tricuspid annulus (tricuspid PA). Interatrial electromechanic delay (EMD) was accepted as lateral PA – tricuspid PA and intraatrial EMD was accepted as septal PA – tricuspid PA.

Statistical analysis

All statistical analysis were done using SPSS 17.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean $\pm$ SD and categorical variables were expressed as percentage. Analysis of normality of the continuous variables were performed with Kolmogorov-Smirnov test. Comparisons between groups were performed by Student's t-test and Mann-Whitney U test, as appropriate. To compare categorical variables, a chi-square test was performed. Pearson correlation analysis was used to test correlations between MPI and atrial

TABLE 1. Characteristics of Sjögren syndrome patients and controls

	Sjögren syndrome (n=40)	Control group (n=25)	<i>p</i> value
Age (years)	47.5±9.8	47.1±9.6	<i>NS</i>
Female gender, n (%)	36 (90%)	21 (84%)	<i>NS</i>
BMI (kg/m ²)	30.9±5.1	28.8±4.7	<i>NS</i>
Hemoglobin (g/dl)	13.7±1.3	13.0±1.2	<i>NS</i>
Creatinine (mg/dl)	0.7±0.1	0.7±0.1	<i>NS</i>
Total cholesterol (mg/dl)	196±37	192±33	<i>NS</i>
LDL (mg/dl)	122±27	114±27	<i>NS</i>
HDL (mg/dl)	46±11	45±11	<i>NS</i>
Triglyceride (mg/dl)	130±60	142±94	<i>NS</i>
hsCRP (mg/dl)	4.4±2.4	-	-
ANA positivity (%)	90.0	-	-
RF positivity (%)	40.0	-	-
AntiRo positivity (%)	60.0	-	-
AntiLa positivity (%)	25.0	-	-
ESSDAI score	1.2±0.9	-	-

(BMI: body mass index, LDL: low density lipoprotein, HDL: high density lipoprotein, ANA: antinuclear antibody, RF: rheumatoid factor, ESSDAI: EULAR Sjögren syndrome disease activity index)

electromechanic properties. Statistical significance was accepted as a *p* value of <0.05.

Results

Forty patients with primary SS and 25 healthy volunteers were included in the present study. Basal characteristics of participants are summarized in Table 1. Mean age was 47.5±9.8 years in the SS group and 47.1±9.6 years in the control group (*p*>0.05). Female ratio was 90% in the SS group and 84% in the control group (*p*>0.05). Body mass index and laboratory parameters including hemoglobin, creatinine and lipid panel were similar between groups.

Extraglandular manifestations were as follows: one patient had renal involvement, two patients had mild peripheral axonal neuropathy and two patients were diagnosed with cutaneous involvement. Of all the patients, 22 patients were receiving hydroxychloroquine, 11 patients were receiving prednisone

TABLE 2. Echocardiographic characteristics of Sjögren syndrome patients and controls

	Sjögren syndrome	Control group	<i>p</i> value
Ejection fraction (%)	64.3±1.8	65.0±1.9	<i>NS</i>
Left atrium (mm)	30.8±3.3	29.8±3.4	<i>NS</i>
Septal wall (cm)	0.80±0.14	0.78±0.11	<i>NS</i>
Posterior wall (cm)	0.72±0.11	0.72±0.11	<i>NS</i>
Deceleration time (msec)	170±24	178±24	<i>NS</i>
E/A	0.9±0.2	1.3±0.3	<0.01
E'/A'	1.0±0.5	1.4±0.6	0.016
cMPI	0.43	0.35	<0.01
tdMPI	0.41	0.32	<0.01
Interatrial EMD (msec)	30.6±10.1	15.4±5.9	<0.01
Intraatrial EMD (msec)	16.4±6.4	5.0±4.5	<0.01
Heart rate (beats/minute)	72±8	73±8	<i>NS</i>

(cMPI: myocardial performance index measured by conventional echocardiography, tdMPI: myocardial performance index measured by tissue doppler echocardiography, EMD: electromechanical delay)

plus hydroxychloroquine therapy, 2 patients were receiving azathiopurine and remaining 5 patients were on no specific therapy. No subjects were using oral muscarinic agents.

Echocardiographic characteristics of groups are summarized in Table 2. Although ejection fractions were similar between the groups, E/A ratios were lower in the SS group. Similarly, MPI values, which were measured by both conventional method and tissue doppler method, were reduced in patients with primary SS.

Atrial electromechanical characteristics of groups are also summarized in Table 2. Interatrial EMD was significantly higher in the SS group compared with the control group (30.6±10.1, 15.4±5.9, respectively, *p*<0.01). Similarly, intraatrial EMD was also prolonged in SS group in comparison with the control group (16.4±6.4, 5.0±4.5, respectively, *p*<0.01). There was no significant relationship between SSA and SSB antibody positivity and MPI and atrial electromechanic properties.

Discussion

In the present study, myocardial functions and atrial electro-mechanic characteristics were investigated in primary SS patients. MPI is increased in primary SS and there is significant atrial electromechanical delay in this patient group, compared with the control group.

Sjögren syndrome is one of the systemic autoimmune diseases that primarily affects exocrine glands but can also have a variety of different organ involvement. [1] Although there have been many studies describing the characteristics of cardiac involvement of systemic autoimmune diseases, there is little known about the effects of SS. For example; Alpaslan et al. conducted a study on RA patients and found left ventricular diastolic dysfunction in this patient group. [20] Plazak and his colleagues showed that left ventricular dysfunction may be more prevalent in a spectrum of different autoimmune diseases. [14] Rosato et al. found regional diastolic dysfunction by tissue doppler echocardiography in patients with systemic sclerosis (SSc) and Paradisp et al. showed disturbed left ventricular filling patterns in SLE patients. [21,22]

It is clear that left ventricular dysfunction is relatively frequent in inflammatory autoimmune diseases. Myocardial dysfunction can be a result of myocarditis, myocardial fibrosis, vasculitis or microvascular dysfunction in these patients, but it can also be secondary to general subclinical or clinical inflammatory status. [14,23-26] Liang et al. showed that diastolic dysfunction is much more prevalent in patients with RA and they concluded that this may potentially be due to chronic autoimmune inflammation. [27] They found a significant relationship between IL-6 and left ventricular diastolic dysfunction. Rosato et al. proposed immunoinflammatory damage as one of the causes of myocardial dysfunction in SSc. [21] The relationship between inflammation and myocardial dysfunction was also investigated in different patient groups. Lee et al. found a significant relationship between inflammatory status and left ventricular diastolic dysfunction, and they proposed that TNF- α may aggravate diastolic dysfunction. [13] Pentraxin 3, which is a novel inflammatory marker, has also been shown to be significantly increased in the presence of left ventricular dysfunction and diastolic heart failure. [28] In our study, the causes of myocardial dysfunction in SS patients were not investigated; rather, the characteristics of left ventricular functions were evaluated in our patient group. From a mechanistic point of view, the inflammatory mechanisms in the pathophysiology of SS may play a role in myocardial dysfunction.

In our study, the atrial electromechanic characteristics showed significant atrial electromechanic delay (AEMD) in patients with SS compared with the healthy control group.

Because increased AEMD is a predictor of atrial fibrillation, patients with SS may be more prone to this kind of arrhythmia. Similar results were also found in other autoimmune diseases. Stojanovich et al. investigated autonomic functions in patients with RA, SLE, SSc and primary SS and they found cardiac autonomic dysfunction in these patients. [29] Aktoz et al. showed significant AEMD in patients with SSc compared with the control group. [30] The increased AEMD in our patient group might be result of disturbed myocardial functions and the results of a study by Yavuz et al., which show that diastolic dysfunction is closely associated with atrial electromechanical characteristics, support our hypothesis. [31]

Because there are few reports regarding the relationship between the anti-SS-A antibody and QT prolongation, we thought that there may be relationship between anti SS-A antibody and atrial electromechanical properties or myocardial functional parameters, [32,33] but no significant relationship was found between the anti-SS-A/SS-B antibodies and atrial electromechanic and myocardial functional properties.

There are some limitations of our study. First, participant number is relatively low. Second, the inflammatory markers that could play role in myocardial dysfunction were not measured. The aim of our study was to investigate myocardial and atrial electromechanical functions, and not to find the causes of myocardial dysfunction. In conclusion, myocardial functions are disturbed and there is significant AEMD in patients with primary SS. Clinical and prognostic significance of AEMD prolongation and subclinical myocardial dysfunction cannot yet be defined. These findings are important because this study is the first to detail myocardial dysfunction and atrial electromechanic delay in primary SS patients.

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